these pilot data are unfortunately inconclusive. As centers have adopted the RCP technique as a standard of care, these data support the need for a multicenter randomized clinical trial to compare safety and neurodevelopmental outcomes of RCP with those of DHCA before broad institutionalization on RCP.

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## Discussion

**Dr Frank L. Hanley** *(San Francisco, Calif).* Thank you. I have no conflicts.

I congratulate Dr Goldberg and her colleagues for a very timely study and for an excellent manuscript and presentation. Sorting out the relative neurodevelopmental morbidity of DHCA and continuous cardiopulmonary bypass in neonatal heart surgery is a major challenge. As the authors imply, this is almost impossible to achieve in a single-institution study. An important contribution of this study, however, is that it may act as a catalyst for further thought and possibly for multi-institutional analysis. I have two comments to make and then a couple of brief questions, and I hope you can bear with me. Most of them relate to technique because technique is so important in neurodevelopmental outcome in terms of what we do in the operating room as we are learning more and more.

The first comment relates to some very detailed technique issues. I hesitate to dwell on these in this forum, but I believe they are important. There are many ways to do RCP, and the details of how it is done can affect the likelihood of neural injury. The technique used in this study, using a polytetrafluoroethylene graft, which is cannulated for RCP, requires a number of minutes of little or no innominate artery perfusion during which the actual graft is being attached onto the innominate artery. In addition, the technique requires, at least as I understand it, several periods of DHCA, one when the central cannula is transferred into the graft, one when the cannula is brought back to its central position after most of the operation is done, and then when the cardioplegic solution is given, because it is given through that same cannula. So this involves three separate periods of circulatory arrest. Furthermore, as you mentioned, there is another obligatory period of very low unphysiologic flow, 5 $mL \cdot kg^{-1} \cdot min^{-1}$, for some undisclosed period of time. As a result, all RCP patients received a period of circulatory arrest that was significant, a mean of 9 minutes overall in three separate settings, in addition to some unphysiologic flow. How much of this morbidity is found in this RCP group and how it is related to these factors is actually impossible to tell. So that is a major question that will have to be answered over time.

As a point of contrast, another way to perform RCP is to directly cannulate the innominate artery with the arterial cannula at the beginning of the case and to use that throughout. There is no switching or further manipulation of the cannula, no periods of

deliberate unphysiologic low cerebral blood flow, and no periods of circulatory arrest. Cardioplegic solution is delivered directly into the ascending aorta by a separate cannula and angiocath.

The point I am trying to make is not that one is better than the other. We do not know, and I am sure anyone can make an argument that this technique has certain disadvantages as well. However, designing an effective multicenter study and really trying to understand this is going to be a major challenge.

The second comment relates to the maturity of the two techniques. DHCA techniques have been widely used and fine tuned over many decades. RCP has been used much less widely and for much shorter periods of time. Time and experience have made and inevitably will continue to make both techniques safer, but with DHCA we will never get away from the fact that the brain is being starved of nutrients the second the pump is turned off. RCP has not had the benefit of nearly the amount of experience or fine tuning that DHCA has had, and furthermore, its problems and current limitations are easily understood and much more solvable than figuring out how to make the brain happy when there is no blood flow going to it. We are not even close to identifying the ideal way to do RCP at this point in time.

This comment is meant to be general, but it also applies directly to the study. My understanding of the standard technique at the University of Michigan is that DHCA has been used for quite a long time, many decades. So it is a good bet that the authors have pitted their RCP learning curve against their decades long, finely tuned circulatory arrest technique in this study. For all of these reasons, the long-term bet may well be on RCP, but we certainly do not know.

I would invite your responses to those two general comments, and then I have two specific questions.

Why did you use 18°C as your level of hypothermia when there is continuous perfusion? At this level, both the warming and cooling times are substantially increased and therefore overall cardiopulmonary bypass may well be lengthened unnecessarily. This is another variable that certainly has not been worked out but may well need to be addressed. I am just wondering why you picked that same level of hypothermia.

The second question is also technical and it relates to venous cannulation. During your RCP did you use a single venous cannula, which can be cumbersome when you have continuous perfusion, or did you use bicaval cannulation with snares, and did you use a left ventricular vent? I hate to put you in this position because I know you are not a surgeon, but these issues are very important, both in terms of how long you are going to be on bypass, how well you can do the operation, and in terms of embolic phenomena. If you do not have a vent in place with a single venous cannula, you easily can capture air in the ventricle that cannot be removed, and this may have implications as well.

**Dr Goldberg.** Thank you very much, Dr Hanley, for those very pertinent points and excellent questions. As you commented, I am not a surgeon but I will try to address your questions. I know Dr Ohye and Dr Bove are in the room. Please feel free to interrupt me at any time.

To start off with your comments, this is a very difficult group to study. Patients with HLHS have multiple periods of time during their lives where they may have hemodynamic instability or be at risk for things that we think put them at risk for neurodevelopmental abnormalities. You stated that a multicenter study is necessary but would be a challenge. I agree that it will be a challenge for all the reasons you described, including that there are multiple technical issues that need to be resolved regarding the delivery of RCP.

You asked about the timing of DHCA in those patients randomized for RCP. For the patients who were able to continue with the RCP technique, excluding the 3 patients who required conversion to DHCA, the mean time of DHCA was about 7 minutes. There were, as you outlined, three separate brief periods of DHCA, the longest of which is approximately 3 minutes for the delivery of cardioplegic solution. However, I do not suspect that many would argue that a 3-minute period of DHCA would significantly affect neurodevelopmental outcome. There was a single cannula technique used as well.

Now, why use a temperature of 18°C? The reason we decided to continue to cool the patients at 18°C was that if RCP needed to be abandoned, then DHCA could be instituted immediately without any delay. In addition, we had no proof that RCP was actually neuroprotective, and therefore we wanted to take all prudent measures to protect the central nervous system.

**Dr Charles D. Fraser** *(Houston, Tex).* Again, congratulations on a beautifully presented study and for bringing to light the importance of a multicenter trial to try and get at the truth about what many of us feel biased about. I wanted to also embellish on Dr Hanley's thoughts about the actual technique of the RCP.

You stated in your presentation that the perfusion flow rate was 20 $mL \cdot kg^{-1} \cdot min^{-1}$, and a really important question then is how was that decided on and how are we confident that that is an adequate cerebral perfusion rate? In other words, how did you determine adequacy of cerebral perfusion during the bypass period?

**Dr Goldberg.** We decided on the technique early on when we started this study in 2001.When we designed this study, we based our flow rates on the prior studies and descriptions of RCP and data from animal models available at that time. I realize that different flow rates have been used in more recent literature. However, some authors caution that an increased flow rate may increase the risk of cerebral edema. In addition, we are not aware that there have been any studies to suggest that one flow rate is clearly superior to any other. There are all sorts of issues to consider, but we were consistent at aiming at 20 $mL \cdot kg^{-1} \cdot min^{-1}$. The patients were monitored with cerebral oximetry, but in talking with the surgeons, they never needed to modify the flow rate based on the cerebral oximetry data with saturations on RCP maintained between 70 and 90.

**Dr Paul Kurlansky** *(Miami, Fla).* This is not so much a clinical question as an experimental one. As an increasing amount of information is becoming available about the biochemistry of reperfusion injury, I was wondering whether you are aware of any studies in the laboratory, at least, if not clinically, to take the opportunity of the time period of ischemic arrest in the reperfusion model to supply substrates that might ameliorate the reperfusion injury that would occur necessarily at the time of complete reperfusion.

**Dr Goldberg.** Are you asking whether there are any treatments that can be used during RCP to ameliorate reperfusion injury?

**Dr Kurlansky.** Correct, similar to the sort of substrate enhancement approach to cardioplegia.

**Dr Goldberg.** I apologize. I do not know the answer to that question, whether there have been any medications or treatments or perfected cooling or a perfect temperature that would optimize RCP.